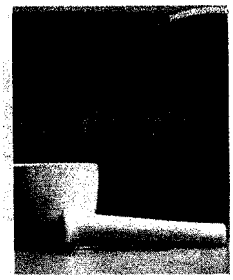

Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

November 5, 1999

Federal Express

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: **Docket Number 85N-0214, 180-Day Generic Exclusivity for Abbreviated New Drug Applications, Federal Register, Volume 64, page 42,873 (August 6, 1999)**

Dear Ladies and Gentlemen:

Reference is made to the Federal Register notice, Volume 64, page 42,873 issued on August 6, 1999 regarding 180-day Generic Drug Exclusivity for Abbreviated New Drug Applications.

Upsher-Smith Laboratories, Inc. hereby submits comments on the regulations recently proposed by the Agency concerning generic drug exclusivity as provided for under 21 U. S.C. 355(j)(5)(B)(iv). Although Upsher-Smith finds much of the proposal to be well conceived and provides much needed clarification, we also find that portions of the proposed regulation are inconsistent with, and/or do not reflect, the intent of the statute.

The underlying intent of the original statute was to provide economic incentive for those companies that challenge existing patents, which provides benefit to the public through the availability of lower-cost alternative medicines. Any regulation, therefore, that has the potential to affect this outcome, must remain consistent with the premise of the statute. Upsher-Smith believes the comments, as set forth in Attachment I, are necessary to support the underlying intent of the original statute.

Sincerely,
UPSHER-SMITH LABORATORIES, INC.

Mark B. Halvorsen, Pharm D.
Director, Clinical and Regulatory Affairs

85N-0214

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UPSHER-SMITH

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Attachment I

Exclusivity Comments
October 19, 1999

Comment 1: 180-day Exclusivity Eligibility, page 42875, section I Background

Proposed Rule:

"Licensing agreements and other arrangements between an innovator company and the generic drug company who is the first ANDA applicant to file a paragraph IV certification can be of considerable financial benefit to the companies involved, but also may contribute to delayed generic competition by forestalling the beginning, or triggering, of the 180-day exclusivity period. These arrangement can create almost insurmountable barriers to the final approval and marketing of generic drug products that are otherwise ready for final approval."

Response:

Although the agreements mentioned may prove to be a potential barrier to market entry for subsequent ANDA applicants, the barriers are not insurmountable. Under the current regulations, mechanisms exist whereby a subsequent applicant(s) may trigger the start of the exclusivity period for the first applicant. This may be accomplished if a subsequent applicant is sued and obtains a favorable court decision. FDA should consider two alternatives to obtaining a favorable court decision; a subsequent applicant could obtain (1) a declaratory judgment of non-infringement or (2) a letter from the innovator stating non-infringement. Either of the two alternatives would trigger the start of the 180-day exclusivity period.

Comment 2: 180-day Exclusivity Eligibility, page 42875, section II.A. 1 Onlv First Applicant is Eligible

Proposed Rule:

"The statutory language describing which applications are eligible for 1 SO-day generic drug exclusivity is ambiguous. The current regulation interprets the statute as allowing eligibility for exclusivity only for the applicant that submits the first substantially complete ANDA with a paragraph IV certification. Although the agency has considered alternative interpretations, such as "rolling exclusivity" in which the next-in-line applicant is eligible for exclusivity should the previous applicant become ineligible, FDA proposes to maintain the current interpretation. The agency, however, invites comments related to exclusivity eligibility, both those supporting this interpretation and those suggesting other possibilities."

Response:

A system where only the first applicant is eligible for exclusivity will potentially encourage applications of lower quality. An applicant that believes they are behind a potential competitor may choose to submit an application of lower quality in hopes that it will be accepted. If the application is initially accepted and later found to be unacceptable (e.g., bioequivalence study not acceptable), a subsequent applicant who puts together a higher quality submission with an acceptable bioequivalence study will be ineligible for exclusivity.

The Agency should consider a "rolling exclusivity". This approach will encourage applications of the highest quality in that applicants will want to ensure that the application is not only acceptable for review but likely to be approved. If the first applicant submits an ANDA of lesser quality, the first applicant runs the risk of not only losing eligibility for exclusivity to a subsequent applicant but also potentially delaying their entry into the market.

Comment 3 : 180-day Exclusivity Eligibility, page 42875, section II.A. 1 Only First Applicant is Eligible

Proposed Rule:
"If the applicant must conduct a new bioequivalence study to obtain approval of the ANDA, the application will not be considered to be substantially complete and the applicant will not be eligible for exclusivity. No other applicant with a paragraph IV certification will be eligible for exclusivity for that drug product,"

Response:
(1) As previously stated in comment 2, this approach could potentially encourage applications of lower quality. In situations where an applicant believes they are behind a competitor, they may attempt to submit an application of lesser quality in hopes that FDA will accept it for review to prevent their competition from receiving an exclusivity period if the application is later refused on the basis of the bioequivalence study design.

(2) If the Agency requests new bioequivalence information due to a change in Agency policy, the applicant with the first paragraph IV certification should be entitled to provide the information requested without losing their eligibility for exclusivity.

(3) With regard to multiple strength products, the exclusivity period for only the strength(s), originally accepted as part of the first applicants' application and subsequently found to have an unacceptable bioequivalence study, should be ineligible for a subsequent applicants' claim to exclusivity. *This ispredicated by the fact that the final rule does not provide for rolling exclusivity.*

Comment 4: 180-day Exclusivity Eligibility, page 42875, section II.A.1 *Only* First Applicant is Eligible

Proposed Rule:

"The first applicant can be the applicant that submits an ANDA that initially contains a paragraph III certification, but later amends the certification to a paragraph IV certification, if at the time of the amendment the applicant's ANDA is the first substantially complete ANDA to contain a paragraph IV certification. If the first applicant subsequently withdraws its application or changes or withdraws its paragraph IV certification, either voluntarily or as a result of a settlement or defeat in patent litigation, no ANDA applicant will be eligible for 180-day exclusivity."

Response:

Voluntary withdrawal of paragraph IV certification or defeat in patent litigation should not result in a loss of eligibility of a subsequent applicant to exclusivity. The approach presented by the Agency does not reward the subsequent applicant for working around the patent or for pursuing the legal challenges to find the original patent in question to be invalid, not infringed, or unenforceable. The Agency should adopt a system of "rolling exclusivity" whereby upon withdrawal of paragraph IV certification or defeat in patent litigation, the next applicant becomes eligible for exclusivity.

Comment 5: 180-day Exclusivity Eligibility, page 42876, section II.A.3 First Applicant Not Eligible if Sued and Loses Lawsuit

Proposed Rule:
"If the first applicant is sued and loses the patent litigation, proposed 3 14.107(c)(IV) would require the applicant to change its certification from a paragraph IV to a paragraph III. Upon the required certification change, the applicant would lose any claim to exclusivity eligibility."

Response:
(1) As previously stated, the Agency should adopt a "rolling exclusivity" to reward the first applicant who successfully designs around the patent or is successful in litigation finding the patent invalid, not infringed, or unenforceable. If the first applicant withdraws its paragraph IV certification or is defeated in patent litigation, the next applicant should be eligible for exclusivity.

Comment 6: 1 SO-day Exclusivity Eligibility, page 42878, section II.B. 1 .a Length of triggering period

Proposed Rule:
"The agency is proposing that the triggering period be 180 days. As described previously, the 180-day period would follow one of the following: (1) The tentative approval of a subsequent ANDA with a paragraph IV certification for the same drug product, (2) expiration of a 30-month stay of ANDA approval due to patent litigation, (3) expiration of a preliminary injunction prohibiting marketing of an ANDA product, or (4) expiration of the statutorily described exclusivity periods for the listed drug.

Response:
The start of the triggering period should not begin until the first applicant with a paragraph IV certification receives approval. Regardless of whether the patent litigation is settled or the 30-month stay of ANDA approval period expires, the triggering period should not begin until the drug product is approved.

Comment 7: 180-day Exclusivity Eligibility, page 42878, section II.B.2 Alternative Length of Triggering Period in Specific Cases

Proposed Rule:

"The agency is considering shortening the length of the triggering period to 60 days in some cases. The 60-day triggering period would apply to an ANDA applicant that already has received final approval at the time of the tentative approval of a subsequent ANDA, and has either not been sued as a result of its patent certification, or has been sued and the case was settled or dismissed without a decision on the merits of the patent claim."

Resoonse:

Depending upon the period of time between the first applicant's approval and a subsequent tentative approval, the 60-day triggering period may pose an unreasonable burden for the first applicant to overcome. It is reasonable to assume that many of the initial paragraph IV certifications will be filed in a short span of time which in turn will likely result in approvals within a short time duration. In those instances, the burden placed on the first applicant to order and receive materials necessary to build launch quantities is unreasonable. The raw materials and packaging components alone may have lead times in excess of 3 months (e.g., printed foil for packaging unit dose). Therefore, for consistency, ease of interpretation and to avoid an unreasonable burden on the first applicant, the triggering period should be set at 180 days.

Comment 8: 1 SO-day Exclusivity Eligibility, page 42879, section II.B.3 Relation&in of Triggering Period to 30-Month Stay

Proposed Rule:

"The generic drug approval process described in the Hatch-Waxman Amendments establishes a 30-month period for resolution of patent litigation resulting from patent certification. During this period, FDA may not approve an ANDA that is the subject of the litigation. After the 30-month period, barring a court order, FDA may grant final approval to the ANDA that is the subject of the litigation. Therefore the agency is proposing that when the first ANDA applicant is sued as a result of its paragraph IV certification and the patent litigation is ongoing, the triggering period would not begin at least until the 30-month period has lapsed. After the 30 months has passed, the triggering period would begin when a subsequent applicant received a tentative approval. If a subsequent applicant received tentative approval during the 30-month stay, the 1 SO-day triggering period would begin on the day the 30-month period expired."

Response:

The 1 SO-day triggering period should not begin until the first applicant receives FDA approval even if the 30-month period has expired. Experience has shown that FDA approval may not happen for 2-3 months after the expiration of the 30-month period. This loss of 90 days could delay marketing of the drug product within the triggering period and ultimately lead to a loss of exclusivity. Therefore, once the 30-month stay of ANDA approval ends, barring any court orders preventing ANDA approval, the 180-day triggering period should not begin, once a subsequent applicant receives tentative approval, until the first applicant receives FDA approval.

Comment 9: 180-day Exclusivity Eligibility, page 42880, section II.E Prompt Approval and Marketing

General Comment:
All ANDA applicants with a paragraph IV certification should be required to promptly notify FDA of any settlements and/or court decisions. FDA should, subsequently, notify the first ANDA applicant that is eligible for 180-day exclusivity of the start of the 180-day exclusivity period if so warranted by any court decisions.

Comment 10: 180-day Exclusivity Eligibility, page 42880, section II.F Declaratory Judgment

Proposed Rule:
"FDA proposes in 3 14.107(f)(2)(ii) that "a decision of a court" should include a nonappealable decision of a court in a declaratory judgment action finding the patent invalid, unenforcable, or not infringed."

Response:
In order to remain consistent with the interpretation the Agency proposed in section II.C. A Decision of a Court, a declaratory judgment should be **any** declaratory judgment finding the patent invalid, unenforcable, or not infringed.

Comment 11: 180-Day Exclusivity Eligibility, page 42881, section II.H Waiver of 180-Day Exclusivity and Relinquishing Eligibility

Proposed Rule:

"Proposed 314.107(e) would permit the ANDA applicant that has obtained 180 days of exclusivity with the occurrence of a triggering event under section 505(j)(5)(B)(iv)(I) or (j)(5)(B)(iv)(II) of the act to notify FDA during the period of exclusivity that it will waive its exclusivity in favor of a subsequent ANDA or ANDA's containing a paragraph IV certification. After receiving such notification, the agency may approve the eligible named ANDA or ANDA's as of the date(s) identified in the notice."

Response:

The act does not address at what stage the first applicant filing a substantially complete ANDA containing a paragraph IV certification may waive its eligibility for exclusivity. Therefore, since the first applicant, by filing the first substantially complete ANDA with a paragraph IV certification, has a contingent interest to receive 180-days of marketing exclusivity, the applicant should have the right to waive exclusivity at any time regardless whether it is waived prior to approval, during the triggering period, or upon the triggering of the exclusivity period. The first applicant should be entitled to benefit from their eligibility for exclusivity. This approach would also benefit the consumer in that in instances where the first applicant is not able, for any reason, to enter the market, generic drug products will potentially be available sooner, thus reducing costs to the consumer.

Comment 12: 180-day Exclusivity Eligibility, page 4288 1, section 11.1 Multiple Strength/Drug Product Exclusivity

Proposed Rule:

"The agency has determined that each strength of a drug product can be independently eligible for exclusivity. Applicants may be eligible for a separate exclusivity period for each particular strength of the drug product in an ANDA when each strength refers to a different listed drug."

Response:

Theeligibility for exclusivity should be tied to the patent. If an applicant submits the first substantially complete ANDA with a paragraph IV certification including only three of four possible strengths, the applicant should be entitled to exclusivity for only those strengths. A subsequent applicant filing a paragraph IV certification covering all four strengths should be entitled to 180-day exclusivity only for the strength not covered by the first applicant. If the different strengths are covered by different patents, the eligibility for exclusivity should only be for those strengths covered by the paragraph IV certification submitted in the application.

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